Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Norelgestromin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredients: Ethinyl Estradiol; Norelgestromin

Form/Route: Film, Extended Release/Transdermal

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.02 mg/24 hr; 0.15 mg/24 hr
   Subjects: Healthy nonpregnant females, general population, who are candidates for hormonal contraception.
   Additional comments: Specific recommendations are provided below.

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2. Type of study: Skin Irritation and Sensitization Study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 0.02 mg/24 hr; 0.15 mg/24 hr (Dose: One-half of a 0.02 mg/24 hr; 0.15 mg/24 hr patch)
   Subjects: Healthy nonpregnant females, general population, who are candidates for hormonal contraception.
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Ethinyl Estradiol and Norelgestromin in plasma (PK study only)

Bioequivalence based on (90% CI): Ethinyl Estradiol and Norelgestromin (PK study only)

Waiver request of in vivo testing: Not Applicable.

Dissolution test method and sampling times: Please note that a **Dissolution Method Database** is available to the public at the Office of Generic Drugs (OGD) website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Multipoint dissolution profiles should be

obtained using a discriminating agitation speed. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until 24 hours and until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Additional comments regarding the PK bioequivalence and adhesion study:

1. Females should not be pregnant. Due to an increased myocardial risk primarily in smokers, non-smoking subjects who have previously used hormonal contraceptives without complications should be enrolled. Also, females weighing less than 90 kg and not exceeding 35 years of age should be considered since older women may be at a higher risk of drug-related adverse events (AEs). Blood pressure (BP) within 140/80 mm Hg limit should be an inclusion criterion.

2. Criteria should also be developed to discontinue subjects that reach a pre-defined maximum BP throughout the study.

3. The patch should be applied to the abdomen in all subjects.

4. Adhesion performance of the intact test product and RLD patches must be formally evaluated and compared in the PK bioequivalence study or in a separate parallel or crossover adhesion study of single 7-day patch applications of the active test product versus the RLD. No patch reinforcement is allowed when the study is being used to establish adequate adhesion performance to support product approval. Adhesion scoring is to be performed at least daily. For patches that completely detach, a score of 4 should be carried forward in the adhesion analysis for all remaining observations in the application period.

5. The recommended scoring system for adhesion of transdermal patches is indicated as follows:

   0 = ≥ 90% adhered (essentially no lift off the skin)
   1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
   2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
   3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
   4 = 0% adhered - patch detached (patch completely off the skin)

6. The Per-Protocol (PP) Population evaluation of the adhesion parameter should be defined per patch instead of per subject as follows:

   Adhesion Analysis – should include all patches except those removed early for unacceptable irritation or those that dropped out of the study before the end of the 7-day application.

7. The cumulative adhesion score and the time from application until patch detachment (i.e., duration of patch wear) should be calculated for the test product and RLD, and a

statistical analysis of the comparative results should be performed. In addition, the following adhesion data should be provided for the test product and RLD:

a. frequency table showing the number of patches with each adhesion score at each evaluation time point
b. number of patches that are completely detached at each evaluation time

The adhesion evaluation of the active test product and RLD must demonstrate that the upper bound of the one-sided 95% CI of the mean cumulative adhesion score for the test product minus 1.25 times the mean cumulative adhesion score for the RLD must be less than or equal to 0. For the adhesion evaluation, the Office of Generic Drugs (OGD) also considers the number of subjects that experience detachment or unacceptable adhesion scores and how early in the application period those unacceptable scores are observed.

The same mean cumulative score could be reached with a small number of high scores (e.g., >/= 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given cumulative score or a given difference between products with regard to mean cumulative scores. Therefore, in addition to cumulative scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of detachment for each product. The proportion of subjects with a meaningful degree of detachment should be no higher for the test product than for the RLD, and detachment should not occur earlier in the application period for the test than for the RLD. To be approved, the test product must be non-inferior with regard to cumulative adhesion scores and also show no meaningful difference with regard to degree of detachment.

8. For the Adhesion Analysis, please provide a separate line listing for each individual test article per subject, per each visit (if data exist), using the following headings, if applicable:

a. Subject identifier
b. Treatment: test article (i.e., test product, RLD)
c. Period (i.e., patch was applied during Period 1 or Period 2)
d. Application Number: number of particular test article application (i.e., 1=first, 2=second)
e. Location of Dose Administration: individual test article application site
f. Number of days since baseline visit
g. Application date and time
h. Date and time of removal or complete detachment
i. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
j. Included in PP population for adhesion analysis (yes/no)
k. Reason for exclusion from PP population for adhesion analysis
l. Scoring date
m. Adhesion scores
n. Identity of the evaluator
o. Was the patch reinforced with tape or overlay (yes/no)

p. If patch was reinforced, time from patch application to reinforcement

Additional comments regarding the skin irritation and sensitization study:

1. The OGD recommends evaluating skin irritation and sensitization in a single study. To support approval, the test product must be no more irritating than the RLD and be no more sensitizing than the RLD. Each parameter is to be evaluated with a separate analysis. The primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study must demonstrate that the test product is no worse than the RLD. The analysis for each parameter and the primary endpoint(s) and any secondary endpoint(s) for each analysis are to be clearly defined in the protocol prior to the start of the study. A clear, objective definition of a sensitization reaction is also to be prespecified in the protocol.

2. Safety concerns preclude the use of two whole, active, 0.02 mg/24 hr, 0.15 mg/24 hr ethinyl estradiol/norelgestromin patches on the same healthy subject during the 21-day skin irritation and sensitization study. The optimum design of this study will depend on the design of the test product patch. Since the RLD has a matrix design that can be safely cut in half, one half of the patch can be used for these studies. If the test product patch also has a design that can be cut to a smaller size, it should also be cut in half and one half of the test product patch applied simultaneously with one half of a RLD patch (to separate skin sites). It would not be acceptable to manufacture a separate batch of product in order to use a smaller patch in this study.

3. Cutting patches will change the shape and size of the patch and may alter the adhesive performance. Therefore, if partial patches are used for the skin irritation and sensitization study, the OGD recommends collecting adhesion data in the PK bioequivalence study to demonstrate that the test product adheres at least as well as the RLD for the 7 day duration of wear. To do so, no reinforcement may be applied to patches in the PK study. Alternatively, a separate single-application parallel or crossover design adhesion study may be conducted for the 7 day duration of wear, comparing the un-altered to be marketed test product and RLD.

4. If the test product patch has a reservoir design that cannot be cut in half, then, in order to avoid an unacceptable risk of serious adverse events, the study should be conducted using a parallel design with healthy subjects randomized to receive either the test product or RLD. The study should be powered to show that the test is no more irritating, no more sensitizing, and adheres at least as well as the RLD.

5. The recommended study consists of two phases, a 21-day Induction Phase, followed by a 14 to 17 day rest period, and a Challenge Phase.

   During the Induction Phase when using one half patches, all test articles (i.e., one half of the 0.02 mg/24 hr; 0.15 mg/24 hr test product[1], one half of the 0.02 mg/24 hr; 0.15 mg/24

[1] The test product evaluated should be the actual patches to be marketed. If the test product has a design that can be cut to a smaller size, the OGD recommends cutting them in half.

hr RLD, optional vehicle patch[2] and optional negative control[3]) are to be applied simultaneously to each subject to clean, dry, intact healthy skin at different sites on the buttock, abdomen, upper outer arm or torso, with sequential patch applications to the same skin sites weekly (i.e., every 7 days; the intended duration of wear) for a total of 21 consecutive days. Thus, it is recommended to apply the patches on Days 1, 8, and 15 to the same sites and to have each of them remain in place for 7 days (a total of 21 days altogether). The Day 15 patches would be removed on Day 22. The irritation evaluation is to be conducted during the Induction Phase, with assessment of "Dermal Response" and "Other Effects" at the time of each patch change.

The Challenge Phase when using one half patches consists of a single 48-hour application of one half of the 0.02 mg/24 hr; 0.15 mg/24 hr test product, one half of the 0.02 mg/24 hr; 0.15 mg/24 hr RLD, optional vehicle patch and optional negative control to a naïve site followed by an assessment of "Dermal Response" and "Other Effects" at 30 minutes and at 24, 48, and 72 hours after challenge patch removal, with a narrative description of any reactions observed, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. A re-challenge test four to eight weeks following the original challenge, conducted in the same manner, is recommended for all subjects with a potential sensitization reaction.

Adhesion should be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization.

6. When evaluating the one half patches, an adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.

7. The irritation and adhesive properties may be sensitive to climate conditions. Therefore, the OGD prefers that the study be conducted in multiple centers with different climate conditions.

8. Subjects should not apply make-up, creams, lotions, powders, or other topical products to the skin area where the patch will be placed, as this could affect adhesive performance or irritation potential.

9. Assignment of the test product, RLD, optional vehicle patch, and optional negative control to skin sites should be randomized. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each application site on each subject.

[2] The optional vehicle patch should have all of the inactive ingredients and be identical to the test product in every manner except for the absence of ethinyl estradiol and norelgestromin.
[3] An example of the optional negative control is an occlusion type device with normal saline applied on a polyester pad within the device chamber.

10. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected by each drug site prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

11. Inclusion Criteria (the sponsor may add additional criteria):
    a. Healthy female subjects 18-35 years of age (inclusive) who are candidates for hormonal contraception.
    b. Subjects who have previously used hormonal contraceptives without complications are the optimal candidates for this study.
    c. Subject willing to stop using any current hormonal contraceptive method.
    d. Subject had a tubal ligation OR throughout the study and for 7 days after completion of the study or premature discontinuation, agrees to abstain from sexual intercourse or use a reliable non-hormonal method of contraception (e.g., diaphragm with spermicide or condom with spermicide).
    e. Negative pregnancy test on first dosing day, prior to application of patch.

12. Exclusion Criteria (the sponsor may add additional criteria):
    a. Subject is pregnant or lactating.
    b. Subject is a current smoker.
    c. Subject weighs 90 kg or more.
    d. Systolic blood pressure >140 mmHg at screening measured in supine position after 5 minutes rest; diastolic blood pressure >80 mmHg at screening measured in supine position after 5 minutes rest.
    e. Subject was previous user of RLD.
    f. Subject who is currently using any long-acting hormonal method of contraception (e.g., contraceptive rod implant such as Implanon™, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera or depo-subQ Provera 104) or has used them within past 3 months.
    g. Subject who currently has any of the following conditions:
        1. Thrombophlebitis, thromboembolic disorders
        2. A past history of deep vein thrombophlebitis or thromboembolic disorders
        3. Cerebrovascular or coronary artery disease (current or past history)
        4. Valvular heart disease with complications
        5. Severe hypertension
        6. Diabetes with vascular involvement
        7. Headaches with focal neurological symptoms
        8. Major surgery with prolonged immobilization
        9. Known or suspected carcinoma of the breast or personal history of breast cancer
        10. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
        11. Undiagnosed abnormal genital bleeding

12. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
13. Acute or chronic hepatocellular disease with abnormal liver function
14. Hepatic adenomas or carcinomas
15. Medical history of condition that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as human immunodeficiency virus (HIV) positive or AIDS, allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, rheumatoid arthritis or systemic lupus erythematosus).

h. Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
i. History of significant dermatologic cancers (e.g. melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the investigative site.
j. Within 3 weeks prior to dosing, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
k. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
l. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application sites, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
m. Presence of open sores at the application site.

13. Criteria should also be developed to discontinue subjects that reach a pre-defined maximum BP throughout the study.

14. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
    a. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. cyclosporine, tacrolimus, adrenocortical steroids such as prednisone, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
    b. Hormonal contraception other than test product and RLD (e.g., oral contraceptive pills, contraceptive vaginal ring such as NuvaRing®, contraceptive rod implant such as Implanon™, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera or depo-subQ Provera 104).

15. Subjects should be informed that wearing patches cut in half will not protect them from pregnancy and they are especially at risk for pregnancy during the first week of the Induction Phase, after Day 7 of the rest period and during the entire Challenge Phase.

16. Subjects should receive the first patch within seven days after the first day of a menstrual period. Subjects currently taking hormonal contraceptives should switch to study drug on the day they are scheduled to start a new contraceptive cycle. This will minimize disruption of the menstrual cycle.

17. Subjects should be advised to expect menstrual bleeding after each patch is removed.

18. Following the Challenge Phase, if a subject wishes to use the contraceptive patch or resume oral contraceptives, she may apply a new (RLD) patch to a different site immediately or start a new pill cycle, but she must also continue using non-hormonal contraception for 7 days after starting the new hormonal contraceptive cycle. Subjects who do not wish to use a hormonal contraceptive may experience vaginal bleeding or spotting after removal of the challenge patch.

19. During the induction phase, subjects should return for weekly visits on Days 8 and 15 for adhesion scoring, patch removal, irritation scoring, and patch replacement and on Day 22 for adhesion scoring, patch removal and irritation scoring. After wearing the challenge patch for 48 hours (or until removal due to intolerable reaction), subjects should return for adhesion scoring, patch removal and irritation scoring at 30 minutes and at 24, 48, and 72 hours after challenge patch removal. Scoring of patch adherence and skin reactions should be performed by a trained and blinded observer at each patch removal. All efforts should be made to ensure that the same scorer is used for all observations. If the same scorer is not used in all cases, inter-scorer variability needs to be addressed in the protocol, specifying the training and standards for each score.

20. Due to likely differences in appearance of the patches, blinding of the observer/evaluator may not be possible, especially for evaluation of patch adhesion, which requires direct observation of the patch itself. However, efforts should be made to blind the evaluation of irritation and sensitization.

21. To ensure adequate adhesion of the test and reference patches in the study, adhesion scores are to be recorded just prior to patch removal. The recommended scoring system for adhesion of transdermal patches is indicated as follows:

    0 = ≥ 90% adhered (essentially no lift off the skin)
    1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
    2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
    3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
    4 = 0% adhered - patch detached (patch completely off the skin)

22. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales[4]:

[4] Berger RS and JP Bowman. A reappraisal of the 21-day cumulative irritation test in man. *J. Toxicol.-Cut. & Ocular Toxicol.* 1982; 1 (2); 109-115.

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

Scale 2: Other Effects

Observation	Score (Numeric equivalent)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the patch site	G (3)
Small petechial erosions and/or scabs	H (3)

When an "Other Effects" score is observed, each score should be reported as a number and letter combination score and also as a numerical total (i.e. numerical "Dermal Response" score + numeric equivalent for the "Other Effects" lettered score).

23. For subjects who experience irritation consistent with a combined score of ≥ 3, or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase and continue with the sensitization part of the study. In this circumstance the highest score observed (not truncated to 3) prior to discontinuation of the first patch site should be carried forward for all remaining observations in the irritation analysis.

24. If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. During the 21-day Induction Phase, if a patch is completely detached for more than 24 hours (unless the patch was removed for an unacceptable degree of irritation), the subject should be excluded from both the irritation and sensitization analyses for that product. During the 48-hr Challenge Phase, if a patch is completed detached for more than 24 hours, the subject should be excluded from the sensitization analysis. The subject should note the date and time of detachment as soon as it occurs. Whereas this study using partial patches can not be used for a definitive assessment of adhesion performance of the active product, criteria may be established for using tape or an overlay to reinforce any patches that are lifting during the irritation and

sensitization study. If the patch is reinforced with tape or an overlay, skin irritation associated with the tape or overlay area should be reported separately from that of the patch application area.

Safety Data and Analyses

25. All application site reactions are to be reported in the data tables and in the detailed narrative description for each subject's response in both phases of this study in the study report. These would include patient complaints such as dryness, itching, burning, pain, or soreness, etc., identifying to which application site the complaint applies. These reports are to be compared between test articles.

26. The safety analyses should include all patients who received a dose of study medication. Safety analyses should include comparing the test product, RLD, optional vehicle patch, and optional negative control with regard to the occurrence and severity of application site adverse events (AEs). Systemic drug-related AEs and concomitant medications are also to be reported but cannot be distinguished between test articles.

Skin Irritation Data Tables and Analyses

27. For each day during the Induction Phase when the skin is evaluated for irritation, please provide a frequency table showing the number of applications of each test article with each combined "Dermal Response" and "Other Effect" score, using Last Observation Carried Forward for subjects who discontinued a test article because of unacceptable irritation. Please refer to Table 1 as an example.

Table 1: Number (%) of Applications by Induction Phase Day and Test Article with a Specific Combined "Dermal Response" and "Other Effect" Score

Induction Phase Scoring Day; Test Article	**Combined "Dermal Response" and "Other Effect" Score**										
	0	**1**	**2**	**2A**	**2B**	**3**	**3A**	**3B**	**3C**	**3F**	**etc.**
Day 8; Test Product											
Day 8; RLD											
Day 8; Vehicle Patch (optional)											
Day 8; Negative Control (optional)											
Day 15; Test Product											
Day 15; RLD											
etc.											

28. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The Per-Protocol (PP) Population for evaluation of skin irritation should be defined as follows:

    Irritation Analysis– the test articles need to be applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect OR if a patch is moved or removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).

29. For each test article (test product, RLD, optional vehicle patch and optional negative control) the mean cumulative irritation score is to be calculated as the sum of all combined "Dermal Response" and "Other Effects" scores observed at each observation divided by the total number of observations.

30. In addition to the cumulative irritation scores, the following data should be provided for each test article:

    a. Total number of observations with a combined "Dermal Response" and "Other Effects" irritation score of 3 or more for each test article.
    b. Number of patches that were moved or removed due to an unacceptable degree of irritation.
    c. Number of days until sufficient irritation occurred to preclude repeat application to the same site.

31. To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0. For the irritation evaluation, the OGD also considers other clinically relevant data including the number of applications that reach a maximal irritation score and the number of subjects that discontinue the product applications because of unacceptable irritation.

    The same mean cumulative score could be reached with a small number of high scores (e.g., >/= 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given cumulative score or a given difference between products with regard to mean cumulative scores. Therefore, in addition to cumulative scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of irritation for each product. The proportion of subjects with a meaningful degree of irritation should be no higher for the test product than for the RLD, and irritation should not occur earlier in the application period for the test product than for the RLD. To be approved, the test product must be non-inferior with regard to cumulative irritation scores and also show no meaningful difference with regard to degree of irritation.

Sensitization Data Tables and Analyses

32. Please provide a frequency table showing the number of applications of each test article during the Challenge Phase with a specific combined "Dermal Response" numerical score and "Other Effect" letter score by each evaluation time point.

33. For all subjects with at least one combined score of 2 or more at 48 or 72 hours after patch removal in the Challenge Phase, please provide a table showing the actual scores for each subject at each evaluation time point during the Induction and Challenge Phases.

34. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The Per-Protocol (PP) Population evaluation of

sensitization should be defined as follows:

> Sensitization Analysis – includes all test articles worn (without any period of detachment longer than 24 hours) for the full 21 day induction phase AND the entire 48-hour challenge phase AND the subject must return for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge patch. If a test article is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.

35. For each test article, individually evaluate each Per Protocol subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the Challenge Phase for potential sensitization. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. Consider a subject to be potentially sensitized if all of the following criteria are met:

    a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
    b. The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
    c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
    d. If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.

    Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization. Provide the total number of subjects considered sensitized to the test product and RLD.

36. The sponsor should provide descriptive statistics comparing the proportion of subjects sensitized or potentially sensitized to each test article.

Adhesion Data Table

37. To ensure adequate skin contact for maximal induction of irritation and sensitization, please provide a frequency table showing the adhesion score for each vehicle patch per study visit. For patches that fall off, provide information about the duration of patch wear before the patch falls off.

Data Submission

38. Study data should be submitted to the OGD in electronic format.

    a. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included.

b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
e. Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

39. Please provide a summary dataset containing a separate line listing for each test article per subject (if data exist) using the following headings, if applicable:

a. Study identifier
b. Subject identifier
c. Site identifier: study center
d. Age
e. Age units (years)
f. Sex
g. Race
h. Name of Actual Treatment (exposure): test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
i. Location of Dose Administration: patch application site
j. Duration of Treatment (total exposure in days) during Induction Phase: time from first application to discontinuation of test article during Induction Phase
k. Duration of Treatment (total exposure in days) during Challenge Phase: time from first application to discontinuation of test article during Challenge Phase
l. Per Protocol (PP) population inclusion for irritation analysis (yes/no)
m. Reason for exclusion from PP population for irritation analysis
n. PP population inclusion for sensitization analysis (yes/no)
o. Reason for exclusion from PP population for sensitization analysis
p. Test article moved (yes/no)
q. Number of times test article moved
r. Test article discontinued (yes/no)
s. Reason for test article discontinuation
t. Adverse event(s) reported for this treatment arm (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDURind	EXDURch	ppirr	ppirr_rs	ppsen	ppsen_rs	mv	mv_n	dis	dis_rs	AErpt
101	1	01	54	YEARS	M	1	A	RUA	21	2	Yes		Yes		Yes	1	No		No
101	1	01	54	YEARS	M	1	B	LUA	21	2	Yes		Yes		Yes	1	No		No
101	2	01	45	YEARS	M	2	A	RUA	21	2	Yes		No	B	No		No		No
101	2	01	45	YEARS	M	2	B	LUA	21	2	Yes		No	B	No		No		No

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Draft dated 7/25/07.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, e.g., M, F, U for Male, Female, Unknown
RACE: Race, e.g. 1, 2, 3, 4, 5 (1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders)
EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=optional vehicle patch, D=optional negative control
EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
EXDURind: Duration of Treatment during Induction Phase (exposure in days; 21 days exposure planned during Induction Phase)
EXDURch: Duration of Treatment during Challenge Phase (exposure in days; 2 days exposure planned during Challenge Phase)
ppirr: Per Protocol (PP) population for irritation analysis, e.g., Y, N (Yes or No)
ppirr_rs: Reason for exclusion from PP population for irritation analysis, e.g., A=prematurely discontinued prior to completing irritation phase due to AE that was not intolerable irritation, B=failed to complete irritation phase due to lost to follow-up, C=failed to complete irritation phase due to subject moved out of the area, etc.
ppsen: PP population for sensitization analysis, e.g., Y, N (Yes or No)
ppsen_rs: Reason for exclusion from PP population for sensitization analysis, e.g., A=prematurely discontinued prior to completing challenge phase due to AE that was not intolerable irritation, B=failed to return for at least one of the two challenge visits at 48 and 72 hours, etc.
mv: Test article moved, e.g., Y, N (Yes or No)
mv_n: Number of times test article was moved, e.g., 1, 2, 3, etc.
dis: Discontinuation of the test article, e.g., Y, N (Yes or No)
dis_rs: Reason for test article discontinuation, e.g., A=irritation, etc.

AErpt: Adverse event(s) reported for this treatment arm, e.g., Y, N (Yes or No)

40. For the Irritation and Sensitization Analyses, please provide a separate line listing for each individual test article per subject, per each visit (if data exist) using the following headers, if applicable:

    a. Subject identifier
    b. Treatment: test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
    c. Application Sequence: number of particular test article application (i.e., 1=first, 2=second, 3=third)
    d. Location of Dose Administration: test article application site
    e. Visit number
    f. Visit date
    g. Number of days since baseline visit
    h. Application day of week (i.e., Sunday, Monday, Tuesday, etc.)
    i. Application date and time
    j. Date and time of removal or complete detachment
    k. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
    l. Reason for exclusion of data from this individual test article from analysis
    m. Scoring date
    n. Induction "Dermal Response" numeric score for each site
    o. Induction "Other Effects" letter score for each site
    p. Challenge "Dermal Response" numeric score for each site
    q. Challenge "Other Effects" letter score for each site
    r. Potentially sensitized (yes/no)
    s. Identity of the evaluator
    t. Individual test article moved (yes/no)
    u. Number of times individual test article moved
    v. Date of each move of individual test article
    w. Individual test article discontinued (yes/no)
    x. Reason for discontinuation
    y. Date individual test article discontinued
    z. Adverse event reported during this visit (yes/no)

    Please refer to Table 3 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 3: Example of dataset containing one line listing for each individual test article per visit per subject

SUBJID	EXTRT	EXSEQ	EXLOC	VISITNUM	SVSTDTC	ELTMBS	day_wk	itaSTDTC	itaENDTC	itaDUR	exc_rs	scr_date	ind_n1	ind_c1
1	A	1	RUA	1	2004-07-01	1	Monday							

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potsens	EVAL	mv	mv_n	mv_dt1	mv_dt2	mv_dt3	dis	dis_rs	dis_dt	AErpt

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Draft dated 7/25/07.

SUBJID: Subject Identifier for the Study
EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= optional vehicle patch, D=optional negative control
EXSEQ: Sequence Number of exposure to particular test article (e.g. application number 1, 2, 3, etc.)
EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
VISITNUM: Visit Sequence Number
SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL: Elapsed Time since Baseline (days)
day_wk: Day of week of individual test article application (i.e., Sunday, Monday, Tuesday, etc.)
itaSTDTC: Individual test article application date and time: start date/time of individual test article
itaENDTC: Individual test article removal date and time: end date/time of individual test article
itaDUR: Individual test article exposure duration (hours) (i.e., time from individual test article application to removal)
exc_rs: Reason for exclusion of data from this individual test article from analysis, e.g., A=subject did not show for appointment, B= test article detached for more than 24 hours, C=protocol/exclusion criteria violation, etc.
scr_date: Scoring date
ind_n1: Numeric “Dermal Response” score for the first site during Induction
ind_c1: Character “Other Effects” score for the first site during Induction
ind_n2: Numeric “Dermal Response” score for the second site (if application site moved due to excessive irritation) during Induction

ind_c2:	Character “Other Effects” score for the second site during Induction
ind_n3:	Numeric “Dermal Response” score for the third site during Induction
ind_c3:	Character “Other Effects” score for the third site during Induction
ch_n1:	Numeric “Dermal Response” score for the Challenge site
ch_c1:	Character “Other Effects” score for the Challenge site
potsens:	Potentially sensitized
EVAL:	Evaluator: identity of the evaluator
mv:	Individual test article moved, e.g., Y, N (Yes or No)
mv_n:	Number of times individual test article was moved, e.g., 1, 2, etc.
mv_dt1:	Date of first move of individual test article
mv_dt2:	Date of second move of individual test article
mv_dt3:	Date of third move of individual test article
dis:	Discontinuation of the individual test article, e.g., Y, N (Yes or No)
dis_rs:	Reason for individual test article discontinuation, e.g., A=irritation, etc.
dis_dt:	Date individual test article discontinued
AErpt:	Adverse Event reported during this visit, e.g., Y, N (Yes or No)

41. Please note that the guidance provided here supersedes information provided in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*, which has been withdrawn. The information given here is general in nature and represents the current thinking of the OGD for this product and may not be appropriate for other transdermal products.

42. Sponsors may submit the protocol for review and comment prior to conducting the study.